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(54) Title: SOLUTION FOR PERITONEAL DIALYSIS AND PROCESS FOR ITS MANUFACTURE			
(57) Abstract <p>A sterile, physiological solution for peritoneal dialysis is prepared by combining, under sterile conditions, at least two solutions comprising a first, sterile glucose solution and a second sterile electrolytes solution both of such volume and concentration, that the final product is both physiologically acceptable and in compliance with pharmacopeic requirements for PD solutions. Optionally, the PD solution further contains nutritional components, such as amino acids.</p>			

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SOLUTION FOR PERITONEAL DIALYSIS AND PROCESS FOR ITS MANUFACTURE

The present invention relates to the production of sterile solutions comprising glucose and in particular ready-to-use solutions for peritoneal dialysis (PD). The process according to the present invention enables the production of sterile glucose containing solutions with little or no contamination of glucose degradation products.

5

Background of the invention

Sterile glucose solutions are commonly used in the medical field. The glucose concentration ranges from 50 to 300 mg/ml and the solutions are used for intravenous (IV) infusion and as peritoneal dialysis (PD) solutions. Peritoneal dialysis is used as a treatment for renal dysfunction, as in acute and chronic renal insufficiency, hypercalcemia, metabolic acidosis and in some cases of intractable oedemas. The major consumption of PD solutions is however in self administered peritoneal dialysis. Whereas out patient dialysis at dialysis clinics is both time consuming and costly, PD can be performed at home, by the patient himself/herself. There are many benefits with PD and this treatment is gaining in popularity.

As IV solution the glucose is administered as a source of energy to a patient, in situations when the patient cannot eat. In a PD solution the glucose functions as an osmotic particle in the solution. The glucose molecule only slowly penetrates the peritoneal membrane. Consequently the concentration gradient draws fluid from the rest of the patient's body into the peritoneal cavity. Whereas an infusion of glucose is performed perhaps once in a lifetime for most patients, at acute illness or trauma, peritoneal dialysis is a lifelong treatment. A normal daily volume is 8 l, which makes about 3000 l annually. Even minor contaminations of the glucose solution must therefor be avoided. For example a contamination of 1 µg/ml amounts to about 15 g over a 5 year period.

Glucose is known to partially degrade to aldehydes, mainly 5-hydroxy-methyl-2-furalaldehyde (5-HMF). Polymerisation of 5-HMF and other degradation compounds results in a brownish hue, known as the caramellisation effect. The degradation of glucose is dependent on time, temperature and pH. At room temperature and low pH the degradation process is slow. At higher temperatures, such as sterilisation temperatures, and at physiological pH the degradation is significant.

However, the only practical way to sterilise a solution is through heat. Normal heat sterilisation or autoclaving is performed at 121 °C at an elevated pressure. The degradation products of glucose are not fully known, but e.g. 5-HMF is assumed to be toxic. This is naturally not acceptable in PD solutions.

30

Commercial glucose solutions have a pH around 4.8 to 5.2. At chronic PD treatment such low pH causes pain and discomfort. It is also assumed that low pH can cause long term effects on the viability of the peritoneal membrane. Therefore manufacturers of PD solutions strive to increase the pH, bringing it closer to physiological pH. The limiting factor is the
5 increase of degradation products, mainly the concentration of 5-HMF, defined in pharmacopeic regulations.

Further, the mass transfer over the peritoneal membranes is influenced by several factors. The transport of liquid and solutes is through the capillary wall, the interstitial space and through the mesothelial cells. The main route is nevertheless the capillary wall but for
10 small molecules, the interstitial space is an important route, specially through so called unstirred layers. The permeability of the peritoneum is surprisingly well preserved with time. However, about 30 % of all patients develop after 3 to 5 years of treatment an increased permeability for small molecules as the permeability for macro molecules remains unchanged. This usually lowers the efficiency of ultrafiltration and thus of the PD treatment as a whole.

15 There are indications that it is the interstitial transport that is affected in CAPD patients. The base substance of the interstices has a gel/sol structure with varying concentration of liquid, i.e. alternating gel and sol areas. The structure of this base substance is dependent of its contents of hyaluronic acid (HA). This can be pictured as fused balls of very elongated molecules (close to 1 mm in length) with high molecular weight ($1 - 10 \times 10^6$
20 kDa). Additionally, this base substance comprises proteoglycans and collagenic and elastic fibres. The main purpose of the HA molecules is to keep water in gel phase. One assumption is, that the this gel layer is leached with time and step-by-step displaced by a harder net of fibrotic character, including channels with free liquid. These channels would then be more permeable for small molecules and perhaps also for water than the normal gel structure. This
25 might be the principal reason for the increased transport of minor solutes in patients with long term CAPD.

Low pH and chemical contamination, e.g. plasticizers, cyclo hexanone and aldehydes (degradation products of glucose) is supposed to have a negative influence on the interstitial tissue. A PD solution more close to physiological properties should thus result in a better
30 preservation of the peritoneal membrane and make it possible for a patient to retain the ultrafiltration function for a longer time. These are important aspects, specially as they influence the wellbeing of the patient both in a shorter time frame and during longer CAPD

treatment. It is well known that un-physiological PD solutions cause pain and discomfort for the patient. In most cases this pain is reduced after a while but in some cases it persists.

WO 93/09820 teaches a double compartment bag, where an acid glucose concentrate is enclosed in one first compartment and a basic salt solution in one second compartment of
5 the same bag, separated by a weld and connected by a tube containing a suitable breakable seal, for example a conventional breakpin. This technical solution is however not satisfactory for several reasons.

Firstly, the double compartment bag is not ready to be used by the patient. The patient is required to break the seal between the compartments and make certain that the two
10 solutions are properly mixed. As many of the patients undergoing PD therapy at home are elderly, this causes many problems. For a number of patients, the breakable seal is difficult or impossible to manipulate. For other patients, mainly elderly, the many steps required, i.e. breaking the seal, mixing the contents and waiting for equilibrium, require too much concentration and effort. In practice, it has been shown that many patients fail to properly mix
15 the contents or forget or are unable to break the seal altogether. This naturally causes discomfort and medical risk for the patient. Secondly, sterilising the acid glucose concentrate in the PVC bags commonly used as PD bags causes potassium stearate to leach from the plastic.

An additional problem, not sufficiently addressed by the technical solutions presently
20 available, is the fact that a large number of PD-patients are malnourished. An optimally composed PD-solution comprising suitable nutrients could help to alleviate the situation. The manufacture of such a solution, comprising both glucose, amino acids and salts is however efficiently hindered by the problems mentioned earlier in this description.

The problem to be solved by the present invention is therefor not only that of
25 sterilisation of easily degraded and/or incompatible constituents in solution and how to avoid unwanted contamination in as large extent as possible, but also to make available a ready-to-use PD solution with beneficial properties, optionally such as nutritive properties. In particular, the invention aims to solve the problem of producing a PD solution, with a minimised content of unwanted degradation products, chemical contamination and
30 physiological or near-physiological properties, causing minimal discomfort to a patient, subjected to PD treatment. Simultaneously, the present invention aims to make available a ready-to-use PD-solution, avoiding the risk of error from the side of the patient. Further, the

present invention aims to make available nutritive PD-solutions, free of unwanted contaminants.

Summary of the invention

The above problems are solved by a process and product as defined in the attached
5 claims. Two or more solutions, constituting components of the final product, are prepared, packaged and sterilised separately. Subsequently, the solutions are joined into one flexible container, under sterile conditions.

Short description of the drawings

The present invention is described in closer detail with reference to the attached
10 examples and drawings, in which

Fig. 1 shows a schematic flow chart illustrating the process according to the invention,

Fig. 2 illustrates a process according to one embodiment of the invention, and

Fig. 3 illustrates a process for large scale production according to the invention.

15 Description of the invention

According to the invention, two or more solutions are prepared, whereof a first solution contains the glucose (A, 1), e.g. in the form of glucose monohydrate. The glucose is mixed with pyrogene free water or water for injections (WFI) and filtrated. The glucose solution is the filled in sealable vessels, suitable for sterilisation and subsequently sterilised,
20 for example autoclaved. Preferably, the glucose solution is filled on glass vessels. A second solution, for example an electrolyte solution (B, 2) or a solution containing nutrients, fats, amino acids etc is manufactured conventionally. The ingredients are mixed in WFI, filtered and the resulting solution filled in sealable vessels, suitable for sterilisation and subsequently sterilised, for example autoclaved. Preferably, the electrolyte solution is filled on glass
25 vessels. Optionally, a third solution (not shown), e.g. a solution comprising essential amino acids, is prepared and filled in vessels, suitable for sterilisation. In preparing the solutions, care has to be taken in choosing the volume, concentration and pH so, that the resulting compounded volume meets the requirements regarding volume, compound concentration and pH.

30 Nutritional IV solutions have been manufactured using a similar technique, i.e. separate manufacture and sterilisation of the components, followed by combining in a process isolator. However, this process has previously not been applied to PD solutions.

Schematically, the manufacture of the glucose solution comprises the following steps:

MANUFACTURING OF GLUCOSE SOLUTION

1. STERILISATION of tanks and pipes, including the filter. Preferably the equipment is steam sterilised ($T > 100^{\circ}\text{C}$, $t > 30$ min).
2. WEIGHT CONTROL of the raw materials
3. MEASURING WFI into the process tank
4. ADDITION OF GLUCOSE into WFI
5. MIXING (In-process control 1)
6. FILTRATION ($0.22\ \mu\text{m}$) (In-process control 2)
7. BOTTLING: Glass bottles are automatically filled and closed with rubber stoppers and sealed with aluminium caps.
8. STERILISATION: The filled bottles are sterilised in conventional manner, e.g. steam sterilised. (In-process control 3)
9. VISUAL CONTROL & LABELLING (QA controls)
10. QUARANTINE: The bottled glucose solution is stored 1 to 2 weeks as a normal quarantine measure. (In-process control 4)
11. RELEASE of the glucose (QC)

Schematically, the manufacturing of the electrolytes solution comprises the following steps:

MANUFACTURING OF ELECTROLYTES SOLUTION

1. STERILISATION of tanks and pipes, including the filter. Preferably the equipment is steam sterilised ($T > 100^{\circ}\text{C}$, $t > 30$ min).
2. WEIGHT CONTROL of the raw materials
3. MEASURING WFI into the process tank
4. ADDITION OF RAW MATERIALS INTO WFI: Sodium chloride, sodium lactate, calcium chloride $\times 2\ \text{H}_2\text{O}$, magnesium chloride $\times 6\ \text{H}_2\text{O}$ are added into WFI.
5. MIXING: The solution is mixed under a nitrogen atmosphere and sodium hydroxide q.s. added. (In-process control 1)
6. FILTRATION ($0.22\ \mu\text{m}$) (In-process control 2)
7. FILLING: Suitable containers are filled with the above solution. The headspace air is replaced with nitrogen and the containers closed.

8. **STERILISATION:** The filled bottles are sterilised in conventional manner, e.g. steam sterilised. (In-process control 3)

9. **VISUAL CONTROL & LABELLING** (QA controls)

10. **QUARANTINE:** The bottled glucose solution is stored 1 to 2 weeks as a normal quarantine measure. (In-process control 4)

11. **RELEASE** of the electrolytes solution (QC)

The in-process controls comprise the following determinations:

In-process control 1: The water for injection is tested for conductivity $<1.0 \mu\text{S}$ and pH 5.5 – 7.0.

In-process control 2: The glucose solution is tested for concentration: optical rotation 98-105 % and pH 4.5 – 5.5. The electrolytes solution is tested for the following concentrations: chlorides $204 \text{ mEq/l} \pm 5\%$ and lactates $70 \text{ mEq/l} \pm 5\%$. The electrolytes solution pH: 8.8 – 9.2.

In-process control 3: Volume 1000 ml – 1100 ml

In-process control 4: The contents are clear and free of visible particles.

Schematically, the compounding of the PD solution comprises the following steps:

MANUFACTURING OF PD SOLUTION

1. **PREPARATIONS:** The sterile components for the actual batch are collected: glucose solution, electrolytes solution and EVA-bags.

2. **SANITATION:** The surfaces of the components are rinsed.

(Visual control operations)

3. **STERILISATION:** The surfaces of the components are sterilised in a transfer isolator using peracetic acid vapour.

4. **TRANSFER:** The transfer isolator is connected to the operating unit and the components transferred thereto.

5. **COMPOUNDING:** Glucose solution (1000 ml) and electrolytes solution (1000 ml) is filled in EVA bags. The bags are sealed and the final product batch removed via a transfer isolator.

(Visual control – Production)

(Chemical and microbiological controls – QA)

6. **LABELLING**

7. **STORAGE** at 2 – 25 °C.

8. QUARANTINE

9. RELEASE of the final product (QC)

After separate manufacture and sterilisation of the glucose and electrolytes solutions, and optionally further solutions, e.g. in normal autoclaves, the contents are combined in sterile EVA bags (5) under sterile conditions in a process isolator (4). Before this, the following safety measures must be performed: the components containing the sterile solutions are counted and inspected visually, their surfaces sanitised and finally sterilised, e.g. in a portable glove isolator (3). Sterilisation of the surfaces is performed with vaporised peracetic acid. The portable glove isolator is joined to a so called "half suit isolator", in which the compounding is performed. This is a positive pressure type I isolator, e.g. a commercially available isolator from La Calhene, France. The glove isolator is joined to the half suit isolator using a suitable air lock system, e.g. the so called DPTE system.

The glucose solution and the electrolytes solution are poured into sterile EVA bags. Optionally, additional solutions, e.g. solutions containing nutritional components, are added. Air is removed from the bags, whereupon they are closed and sealed. The bags can preferably be initially closed with plastic clips and later heat sealed. The finished bag (6), containing a ready-to-use PD solution is removed from the process isolator (4) using the previously mentioned glove isolator (3) or other suitable air lock system (3')

Naturally, the glucose and electrolytes solutions are controlled visually, chemically and microbiologically before released by Quality Control and transferred to the department where the compounding is performed. The final PD solution should be clear and colourless or slightly yellowish and meeting the requirements of the European Pharmacopoeia (Ph. Eur.), the British Pharmacopoeia (BP) or the United States Pharmacopoeia (USP)

Each batch is controlled and the process isolator is continuously monitored with respect to microbiological contamination during the entire production process. All process isolators are tested and validated with regular intervals.

ExamplesExample 1: Preparation of a glucose solution

To prepare 1 l glucose solution, 50.0 g glucose monohydrate is mixed in 1000.0 ml water for injections (WFI), filtered (0.22 μ m) and filled in glass bottles. The WFI is controlled in-process and guaranteed to meet the following requirements: conductivity <1.0 μ S and pH 5.5 – 7.0. The glucose solution is controlled in-process and guaranteed to meet the

following requirements: glucose, optical rotation 98-105 %, pH 4.5-5.5. The glass bottles are closed with rubber stoppers and sealed with aluminium caps prior to sterilisation. Sterilisation is performed as conventional steam sterilisation. The volume in the vessels is continuously controlled and has to be in the interval of 1000 – 1100 ml. The vessels are also inspected visually and the contents are required to be clear and free of visible particles.

Example 2: Preparation of an electrolyte solution

To prepare an electrolyte solution, sodium chloride (11.34 g), sodium lactate (12.2 ml 50 % solution), calcium chloride 2H₂O (0.514 g) and magnesium chloride 6 H₂O (0.306 g) are mixed in WFI under a nitrogen blanket. Sodium hydroxide is added q.s. and WFI ad 1000.0 ml. The solution is filtered (0.22 µm) and filled in glass bottles. Before filling the solution is controlled in-process and guaranteed to meet the following requirements: chloride content: 204 mEq/l ±5%, lactate content: 70 mEq/l ±5%, and pH 8.8-9.2. The headspace air is replaced with nitrogen and the bottles closed and sealed, prior to sterilisation. Sterilisation is performed as conventional steam sterilisation. The volume in the vessels is continuously controlled and has to be in the interval of 1000 – 1100 ml. The vessels are also inspected visually and the contents are required to be clear and free of visible particles.

Example 3. Compounding the PD solution

The previously prepared glucose solution and electrolyte solution, packaged in 1000 ml bottles and sterilised is collected in equal volumes, in this case 1000 ml each. A sterile EVA-bag with the volume 2 l is reserved for the compounding. All items are rinsed and placed in a transfer isolator, where they are surface sterilised using peracetic acid vapour. The transfer isolator is connected (DPTE) to a process isolator.

The containers containing the glucose and the electrolytes solution are opened and the contents poured into the EVA bag. Surplus air is removed from the bag which is closed first with a plastic clip, then heat sealed. The sealed containers are removed from the process isolator through a suitable air lock, maintaining the sterile conditions of the process isolator.

Example 4. Compounding a nutritive PD-solution

Separately produced and sterilised solutions, a first solution containing glucose, a second containing electrolytes and a third containing essential amino acids are transferred to a process isolator in unbroken packages. Before entering the process isolator, the packages are taken through an air lock, in which their surfaces are sterilised. The packages are then opened and the three solutions combined in EVA bags, as described in the previous example.

Example 5. Large scale production of PD-solution

According to one embodiment of the invention, the first and second solutions and optionally a third solution, are sterilised in bulk containers, e.g. large stainless steel vessels (1 and 2 in fig. 3). Said vessels are before sterilisation equipped with closed conduits (1' and 2'). When the contents are sterilised, said conduits are brought to enter a process isolator (4) under sterile conditions. The outside of the conduits is sterilised before entry into the process isolator. Inside the process isolator, under sterile conditions, the conduits are opened and the solutions measured and mixed in EVA-bags (5), as described in the previous examples.

Although the invention has been described with regard to its preferred embodiments, which constitute the best mode presently known to the inventors, it should be understood that various changes and modifications as would be obvious to one having the ordinary skill in this art may be made without departing from the scope of the invention which is set forth in the claims appended hereto.

15 —

Claims

1. Process for the production of a sterile, physiological solution for peritoneal dialysis, characterized in that said solution is produced by combining under sterile conditions two or more separately prepared and sterilised solutions whereof one is a glucose solution and the other is an electrolytes solution.

2. Process according to claim 1, characterized in that said combining of two or more separately prepared and sterilised solutions is performed in a process isolator (4).

3. Process according to claim 2, characterized in that said two or more solutions are filled in glass vessels, sterilised and introduced in a process isolator (4), where the contents are combined in EVA-bags (5).

4. Process according to claim 1, characterized in that the first glucose solution has a pH value of 4.5 to 5.5 and the second electrolytes solution has a pH value of 8.8 to 9.2.

5. Sterile, physiological solution for peritoneal dialysis, characterized in that the solution has a pH in the interval of 6.5 – 7.5 and a glucose concentration in the interval of 2 – 2.5 %.

6. Sterile, physiological solution for peritoneal dialysis, characterized in that the solution comprises glucose, electrolytes and amino acids.

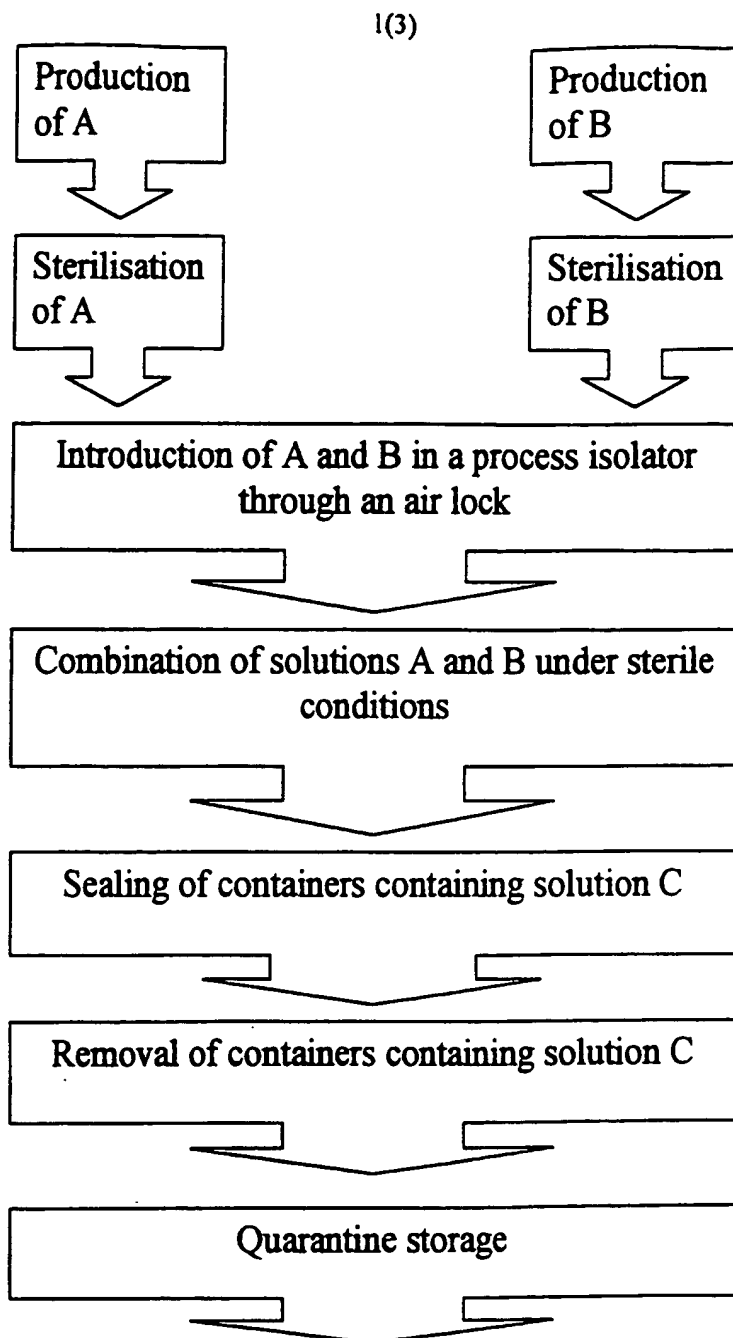
7. Sterile, physiological solution for peritoneal dialysis, characterized in that said solution is produced by the process according to any one of claim 1 – 4.

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AMENDED CLAIMS

[received by the International Bureau on 15 March 1999 (15.03.99);
original claims 1-7 replaced by amended claims 1-6 (1 page)]

1. Process for the production of a ready-to-use sterile, physiological solution for peritoneal dialysis, characterised in that said solution is produced by combining under sterile conditions two separately prepared and sterilised solutions in a process isolator (4), one
5 of which is a glucose solution and the other one an electrolyte solution.
 2. Process according to claim 1, characterised in that two or more solutions are introduced into glass vessels, sterilised, and introduced into a process isolator (4), in which the contents are combined in EVA-bags (5).
 3. Process according to claim 1, characterised in that the glucose solution has
10 a pH value of 4.5 – 5.5 and the electrolyte solution has a pH value of 8.8 – 9.2.
 4. Ready-to-use Sterile, physiological solution for peritoneal dialysis, characterised in that the solution has a pH in the interval of 6.5 – 7.5 and a glucose concentration in the range 2 – 2.5 %.
 5. Ready-to-use sterile, physiological solution for peritoneal dialysis, characterised
15 ised in that the solution comprises glucose, electrolytes, and amino acids.
 6. Ready-to-use sterile, physiological solution for peritoneal dialysis, characterised ised in that said solution is produced by the process according to any one of claim 1 – 3.
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**Fig. 1**

2(3)

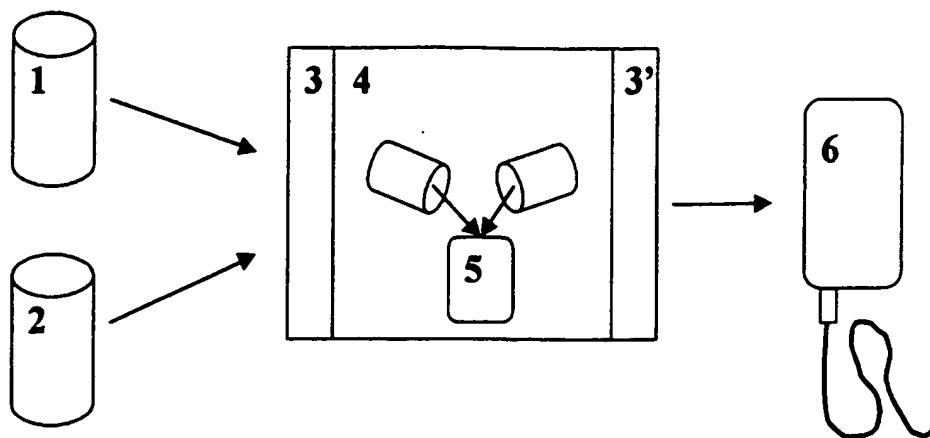
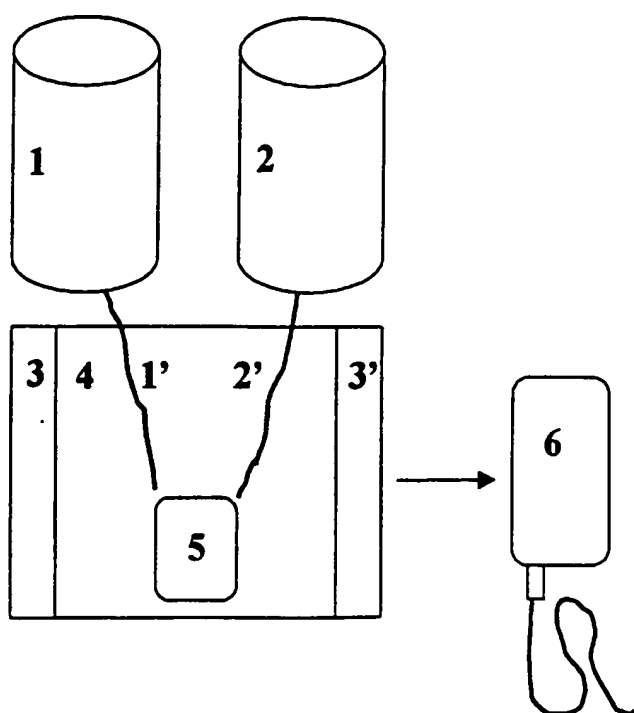


Fig. 2

3(3)

**Fig. 3**

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/01831

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/08, A61K 31/70, A61M 1/28, A61J 1/10
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K, A61M, A61J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 9705852 A1 (GAMBRO AB), 20 February 1997 (20.02.97)	1-5,7
A	--	6
Y	WO 8203773 A1 (BAXTER TRAVENOL LABORATORIES, INC.), 11 November 1982 (11.11.82)	1-5,7
X	--	6
A	WO 9309820 A1 (GAMBRO AB), 27 May 1993 (27.05.93)	1-7

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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INTERNATIONAL SEARCH REPORT
Information on patent family members

01/12/98

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PCT/SE 98/01831

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